2007 Small Business Pharmaceutical Workshop

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Patricia L. Alcock
Deputy Director
Division of Field Investigations
Office of Regulatory Affairs
FDA

Mastering Regulatory Compliance

- **A Question -**
  - Who runs the shop?
  - Who oversees the operations?
  - Who has final authority and approval?

Organization / Department ?

- Production
- Validation
- Engineering
- Quality Control Unit
- Regulatory Affairs

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- Let us consider your Shop - *Home town, USA*
  - *Small shop*
  - *Not to large shop*
  - *One of the big guys*

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- Type of finished products e.g.,
  - Sterile/non-sterile
  - Solid oral dosage
  - Liquids
  - Large volume or small volume parenterals
- Type of manufacturing operations e.g.,
  - Active pharmaceutical Ingredient, (API)
  - Aseptic filling
  - Isolator technology
  - Mixing, Blending, Isolation, Purification

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- Some of the manufacturing steps are:
  - Critical steps ?
  - Important steps ?
  - Less important steps ?
  - Required steps?

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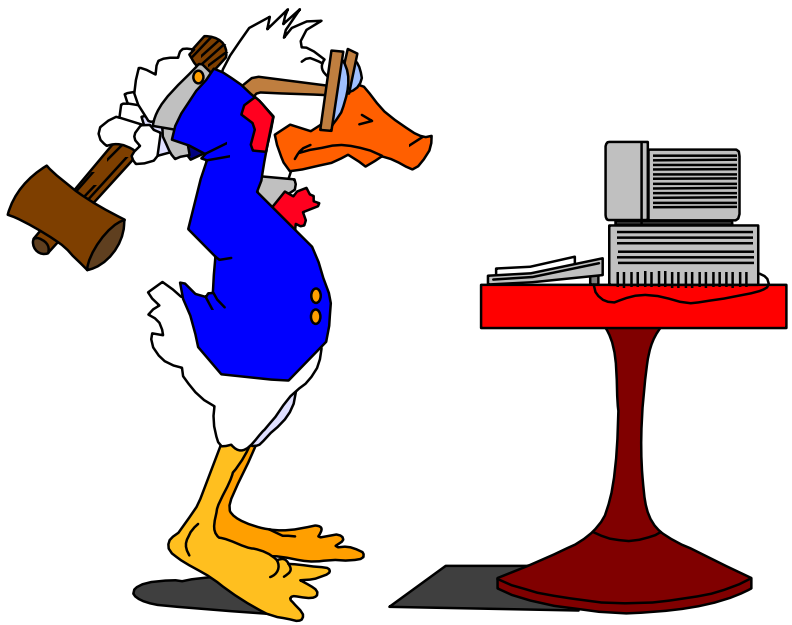
- Does your process use computer assisted automation?
  - Fully - automated
  - Semi - automated
  - Non - automated



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- What are the Quality Control analytical test requirements?
  - In-process control checks
  - Chemistry/Microbiology
  - Finished product QC test requirements / specifications
  - Stability Tests

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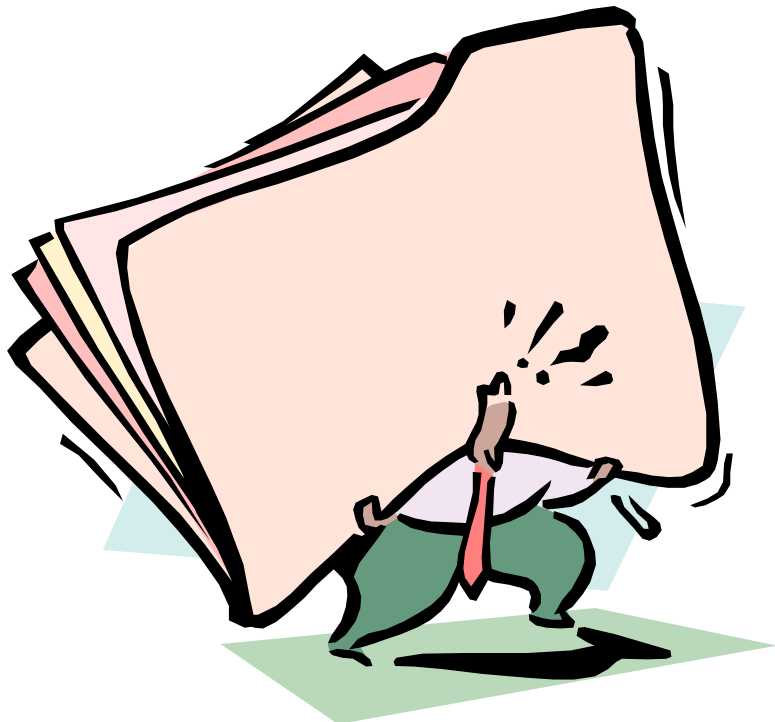
- How much information is needed?
- Type of info / data e.g.,
  - Process Validation
  - QC analysis
  - Data to support manufacturing operations



FDA defines Process Validation

- *Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.*

Process Validation

- Let’s put the legal jargon aside for a moment.
- I like simplicity. How about the following thought?

Validation

"*In today's pharmaceutical industry, whether you are thinking about a computer system, a water treatment systems, or a manufacturing process, validation means nothing more that well-organized, well-documented* common sense*."*

Kenneth Chapman

Director Quality Assurance Pfizer, Inc.

A *History of Validation in the United States*

Pharmaceutical Technology, 10/91

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- When you go back to your shop ask your staff, (e.g., operator/analyst), the following 2 questions and 1 request.

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- Question #1- ***What do you do?***

  Specifically, what needs to be executed to accomplish the manufacturing steps or QC analysis?

- ***Examples -***
  - Weight out raw materials;
  - Maintain proper operation of the Water System;
  - Perform qualifications of production or laboratory equipment;
  - Aseptic processing
  - QC Analysis

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- Question #2 – ***How do you do it?***

  Specifically, how do you perform the manufacturing steps or QC analyses that need to be accomplished?

- ***Examples –***
  - Follow Standard Operating Procedures
  - Written Protocols
  - Pharmacopoeia methods
  - National or International Standards, (e.g., AAMI, ISO)

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- Request #1-
  - ***Show me.***
- That is:
  - ***Show me*** what
  - ***Show me*** how
  - ***Show me*** the data to support successful execution of the manufacturing steps
  - ***Show me*** the analytical data

What does the question do for you?

Question #1-

What do you do?

For, the individual who did the work, (e.g., Operator, Analyst, Technician).

1. Individuals will describe their normal day-to-day operation.
2. This also assist to demonstrate the individuals' level of knowledge and comprehension of their respective jobs.
3. Or, they may describe some inconsistencies with current established procedures.

What does the question do for you?

Question #2 –

How do you do the work?

For, the individual who did the work, (e.g., Operator, Analyst, Technician).

1. The written SOP describe the specific work required to be performed.
2. The SOP is complete and accurate.
3. The SOP may not be current and does not accurately describe the steps performed.

What does the question do for you?

<u>Question #2 cont. –</u>

How do you do the work?

For, the individual who did the work, (e.g., Operator, Analyst, Technician).

1. Individuals are executing the specified operations as described in established protocols.
2. The manufacturing steps are successfully executed with the required specifications and acceptance criteria achieved.
3. Individuals may be performing the requisite operations in an inconsistent manner as described in the protocols.

What does the request do for you?

Request #1 –

Show me.

For, the individual who did the work, (e.g., Operator, Analyst, Technician).

1. The data supports the manufacturing steps and QC analysis.
2. The data supports the successful execution of the defined specifications described in protocols.
3. Or, the data documents manufacturing inconsistency, or does not support the requisite production steps and the QC analysis.

Some times…

The SOPs are written just short of the preamble to the Constitution.

Some times…

"We the people of the great sovereign domain we call Production with our brothers and sisters from the far away, never, never land called Quality Control Laboratory promise to come together everyday, or as much as we dare to tolerate (which ever comes first), to do everything for everyone at all times so help us, us."

Some times…

- The established procedures are not followed.
- The SOP is not complete or accurate.
- Specifications established in protocol acceptance criteria are not met.

So then….

- Assure that the written procedures and protocols are complete and accurate;
- Assure that personnel are following all of the requisite manufacturing steps as described in the SOP or protocols;
- Assure that laboratory analyst are performing the appropriate methods of analysis, (e.g., pharmacopeias compendia).

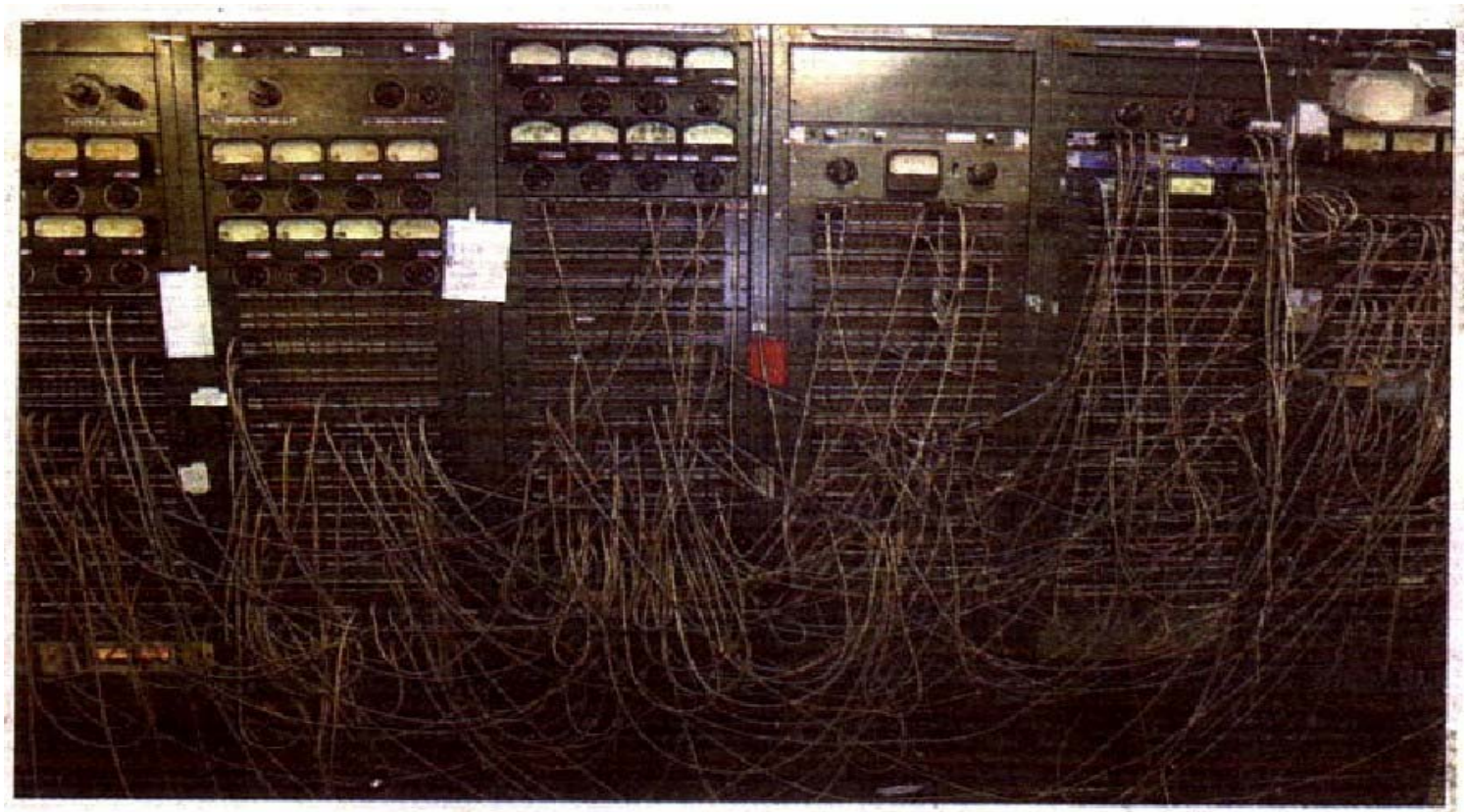
Some times…we drop the ball

- How do we correct the issues or concerns?
- In response to the issues or concerns, were the corrective actions appropriate?
- Are concerns or deviations addressed within a reasonable period of time?

Changes

- There may be changes, (e.g., adjustments, refinements), to the manufacturing operation.
  - Minor
  - Major

In the event of changes…



Photos by RUTH FREMSON/The New York Times

A maze of old, cloth-covered cables makes up a switchboard system in the Audio Master Control room at the United Nations in New York City.

In the event of changes…

- Are the changes major or minor?
- How do you determine if the changes are major or minor?
- Who do you ask?
- There are knowledgeable individuals who can determine if changes are major or minor.

In the event of changes…

- Do the changes impact upon the finished product or manufacturing process?
- How do you determine the impact of changes?
- There are knowledgeable individuals who can determine if major or minor change impact the finished product or manufacturing process.

In the event of changes…

- The individual changes, when considered collectively, do they present a departure from the validated process or equipment qualifications?
- Who do you ask?
- There are knowledgeable individuals who can determine if the changes, collectively, do not impact upon the validated process or equipment qualifications.

In the event of changes…

- Do the changes require a Supplement to be sent into the Center?
- Or, can the changes be included in an annual product review?
- Who do you ask?
- There are knowledgeable individuals who can determine if a supplement is required.

Changes require assessment

- Who do we ask in order to answer the questions?
- The knowledgeable individuals;
  - Production
  - Validation
  - Engineering
  - Quality Control Unit
  - Regulatory Affairs

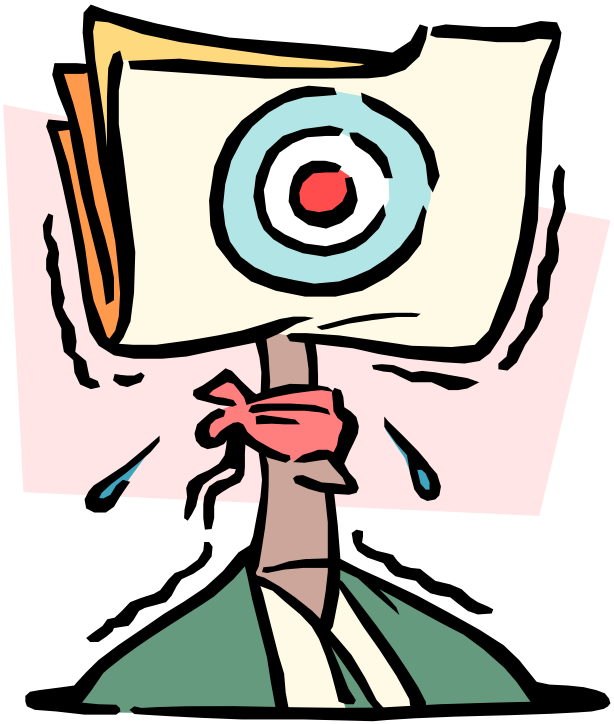
Changes require assessment

- The knowledgeable individuals may employ a variety of evaluation tools to determine impact of the changes and if there are operational or regulatory risks.
- For example:
  - Faulty Tree Analysis, (FTA)
  - Failure mode and effect analysis, (FEMA)
  - Hazard Analysis Critical Control Points, (HACCP)

Changes require assessment

- What if there is no formal evaluation tools, (i.e., the examples in the preceding slide)?

Not to worry…



- Your currently performing;
  - Evaluations
  - Assessments
  - Determining the impact and/or risks
  - Providing recommendations

Not to worry…remember..

- What you do, how you do it, and the supporting data is in a *Change Control* documents, SOP or protocol.
- The document describes and answers many questions concerning the ***evaluation process*** and ***rationale*** to support the major or minor changes and there impact upon the manufacturing process.

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- The Code of Federal Regulations (CFR) describe a number of responsibilities requirements, and oversight activities of...
- The Quality Control, (QC), Unit

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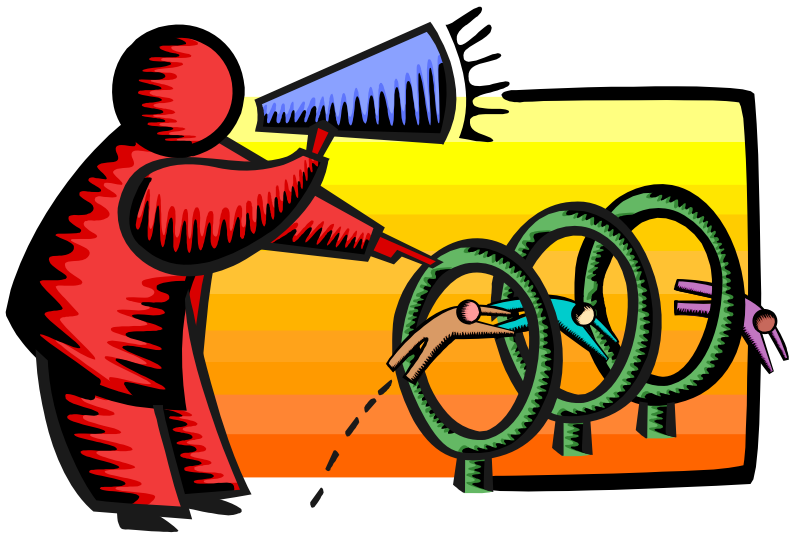

- A successful QC Unit obtains assistance, knowledge, and support from:
  - Senior Management
  - Production
  - Validation
  - Engineering
  - Quality Control laboratory
  - Regulatory Affairs

Recommendations for NDA/ANDAs September 2003 – April 2004

- Inadequate QA Functions 2%
- Inadequate SOP 2%
- Facility withdrawn – 3%
- Previous Deviations persists 7%
- Inadequate Lab controls 7%
- Drug not made at site 8%
- Contamination 13%
- Others 15%
- Pending Regulatory Action 18%
- Firm Not Ready 25%

Surfin' the FDA Internet

- Human Drugs:
  - http://www.fda.gov/cder
- Biologics:
  - http://www.fda.gov/cber
- Devices:
  - http://www.fda.gov/cdrh
- Vet Drugs:
  - http://www.fda.gov/cvm

Contact Information

Patricia L. Alcock
Deputy Director
Division of Field Investigations
Office of Regional Operations
Office of Regulatory Affairs
FDA
Tel: 301-827-5653
Fax: 301-443-3757
Email: Patricia.Alcock@fda.hhs.gov